Neuropharmacology 93 (2015) 164–170

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

# Involvement of NMDA receptor subtypes in cortical spreading depression in rats assessed by fMRI

Artem Shatillo [a, *], Raimo A. Salo [a], Rashid Giniatullin [a, b], Olli H. Gröhn [a]

[a] Department of Neurobiology, A. I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Neulaniementie 2, Kuopio 70700, Finland
[b] Lab of Neurobiology, Kazan Federal University, 18 Kremlyovskaya St., Kazan 420008, Republic of Tatarstan, Russian Federation

ARTICLE INFO

*Article history:*
Received 28 August 2014
Received in revised form
23 December 2014
Accepted 26 January 2015
Available online 14 February 2015

*Chemical compounds studied in this article:*
Dizocilpine, MK-801 (PubChem CID: 180081)
Ifenprodil (PubChem CID: 11957579)
TCN-201 (PubChem CID: 4787937)

*Keywords:*
Spreading depression
BOLD
fMRI
Glutamate
NMDA receptors

ABSTRACT

Cortical spreading depression (CSD) is a phenomenon implicated in migraine with aura and associated with other neurological disorders (e.g. stroke, brain trauma). Current evidence points to the essential role of NMDA receptors in CSD mechanisms. However, the roles of multiple subunits of NMDA receptors expressed in neurons, glia and blood vessels *in vivo*, are little explored. Using BOLD fMRI of urethane anesthetized rats as an integrative CSD readout, we tested the involvement of different NMDA receptor subtypes in CSD induction and propagation. Rats were treated with a non-selective NMDA blocker (MK-801), NR2B antagonist (ifenprodil) or a NR2A selective antagonist (TCN-201). CSD was induced during fMRI scanning by application of KCl onto the cerebral cortex and fMRI data were collected by 9.4 T MRI. The non-specific NMDA antagonist MK-801 completely blocked CSD, which was not observed in the NR2A group where TCN-201 did not alter the CSD features. Unexpectedly, the NR2B specific antagonist ifenprodil largely promoted the initial negative phase of the BOLD CSD response, likely due to altered neurovascular coupling. Our data suggest key roles and differential involvement of NMDA receptor subtypes in CSD generation and propagation, highlighting an important role for the NR2B subtype.


## 1. Introduction

Cortical spreading depression (CSD) is a self-propagating wave of neuronal depolarization (Leao and Morison, 1945; Leao, 1944) with glial and vascular involvement. (Charles and Baca, 2013) CSD is associated with the massive release of various neurotransmitters, dramatic shifts in ionic gradients and essential blood flow. (Smith et al., 2006) CSD takes place in a number of major neurological disorders including stroke, brain trauma and notably, in migraine with aura. (Dreier, 2011; Lauritzen et al., 2011). The primary role of CSD in migraine with aura (MWA) was hypothesized by Leao and Morrison (1945), Milner (Milner, 1958) and later confirmed, using the planar intracarotideal 133-Xenon method, SPECT and PET (Lauritzen, 1994; Olesen et al., 1981; Woods et al., 1994). Observation of CSD in MWA patients was also done using functional MRI (Hadjikhani et al., 2001).

The excitatory neurotransmitter, glutamate, acting through via ionotropic N-methyl-D-aspartate (NMDA) receptors, is currently recognized as a key contributor to CSD induction and propagation (Pietrobon and Moskowitz, 2013; Somjen, 2001). For these reasons, NMDA receptors are a promising therapeutic target for clinical use. The NMDA receptor is one of the most abundant receptors in the mammalian brain, expressed in both neuronal and glial tissues (Verkhratsky and Kirchhoff, 2007) as well as in cerebral arteriolar endothelium (LeMaistre et al., 2012; Sharp et al., 2003). The receptor is a heterotetrameric ionotropic channel that is typically comprised of different combinations of NR1 and NR2A-D or NR3A-B subunits (Monyer et al., 1992; Paoletti and Neyton, 2007). In particular, receptors with NR2A subunits normally mediate synaptic transmission whereas NR2B containing receptors are mainly expressed extrasynaptically (Sanz-Clemente et al., 2013) and in astrocytes (Dzamba et al., 2013). A growing body of evidence

* Corresponding author. Tel.: +358 453111767.
*E-mail addresses:* artem.shatillo@uef.fi (A. Shatillo), raimo.salo@uef.fi (R.A. Salo), rashid.giniatullin@uef.fi (R. Giniatullin), olli.grohn@uef.fi (O.H. Gröhn).

http://dx.doi.org/10.1016/j.neuropharm.2015.01.028
0028-3908/